Australian Government
Department of Health
Therapeutic Goods Administration

Therapeutic Goods Administration

An introduction to the work of Australia's regulator of therapeutic goods

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Previous Talk

- Why do we need regulation?
- Who is Australia's regulator?
- How the TGA operates
- Who works at the TGA
- Therapeutic goods
- Australian Register of Therapeutic Goods
- TGA's mission
- The benefit versus risk approach
- Premarket and post market Activities
- Regulation of medicines
- Post-market monitoring

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The regulation of medical devices in Australia

Overview

- What is a medical device?
- Comparing medicines and medical devices
- How does a medical device get to market?
- The benefit versus risk approach
- Risk classification rules
- Statistics on patients requiring medical devices
- In vitro diagnostic tests
- Essential principles
- Conformity assessment
- Quality, Safety and performance
- Regulation of mobile medical “Apps”.

What is a medical device?

The TGA defines a medical device as an instrument apparatus, appliance, material or other article intended to be used for human beings for:

- diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or disability
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

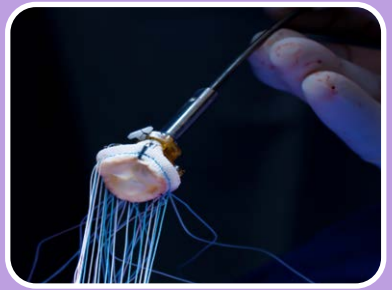
Dressings

Dental implant

Breast implant

Glucose monitor

Comparing medicines and medical devices



A medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means like a medicine or a vaccine

Special rules for particular kinds of medical devices

The *Therapeutic Goods (Medical Devices) Regulations 2002* includes special provisions for combination products

Part 5 in schedule 2-

5.1 Medical devices incorporating a medicine

(1) This clause applies to a medical device of any kind that incorporates, or is intended to incorporate, as an integral part, a substance that:

(a) if used separately, would be a medicine; and

(b) is liable to act on a patient's body with action ancillary to that of the device.

(2) The device is classified as Class III.

For example, Pacemaker leads coated with anti-inflammatories would still be regulated as Medical devices, based on the principal intended action of the pacemaker and ancillary action of the anti-inflammatory.

Further guidance on combination products is provided in the Australian medical devices guidance document number 35 (Device – medicine boundary products)- currently under revision.

How does a medical device get to market?

A sponsor makes an application to include a device on the Australian Register of Therapeutic Goods (ARTG) so that it can be legally supplied in Australia

The applicant must have information available to demonstrate the **quality**, **safety** and **performance** of the medical device

The device must undergo a Conformity Assessment* procedure and comply with the Essential Principles*.

*More information about what this means is provided later in the presentation

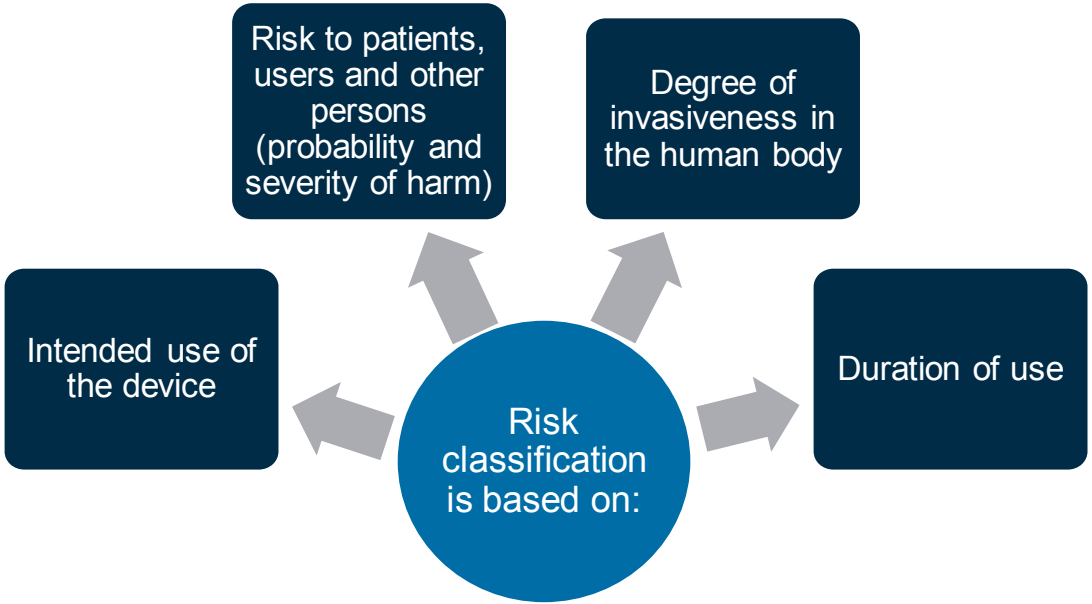
Medical devices can not be tested like medicines in a traditional clinical trial

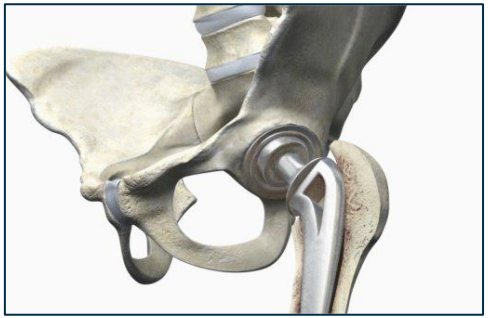
Information on their performance and safety is important prior to market authorisation

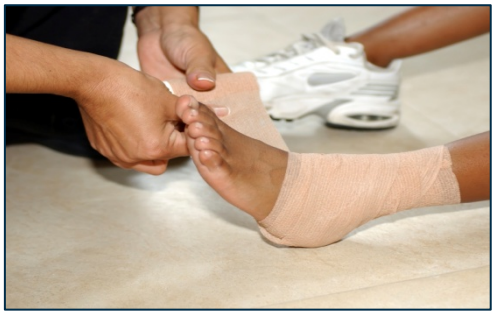
Most new devices are improvements of older versions based on data collected from real life use

Benefit versus risk approach

The level of regulation is based on consideration of:







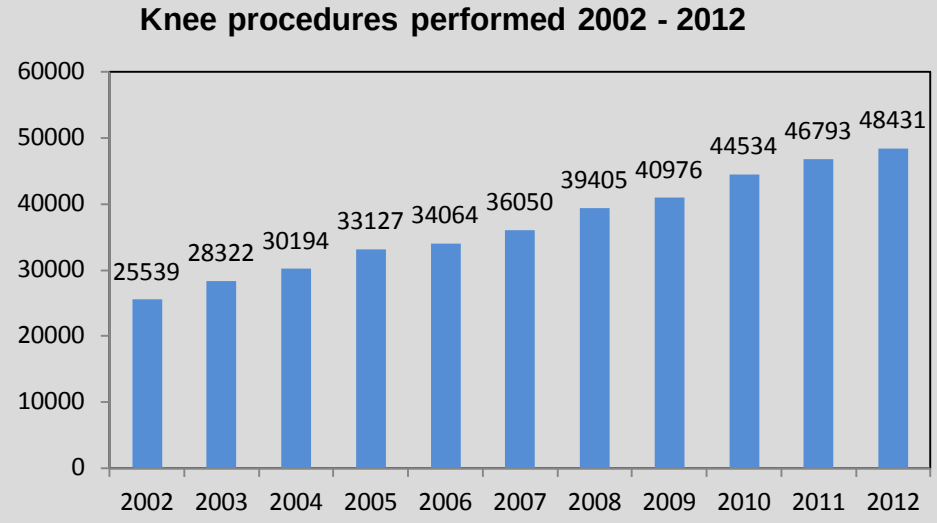
Risk classification rules – medical devices

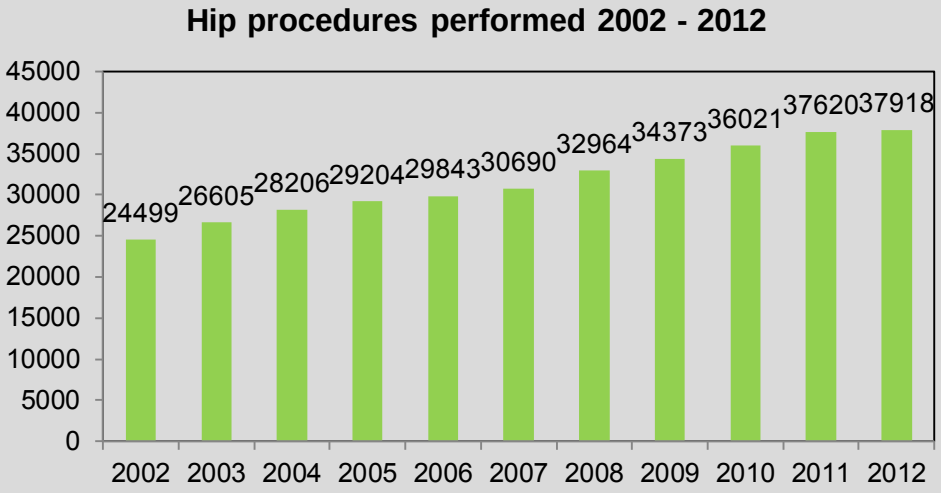
Lower risk

Higher risk

Medical device classification	Example
• Class I	• Urine collection bottles
• Class Is (intended to be supplied sterile)	• Sterile adhesive dressing strips
• Class Im (with measuring function)	• Clinical thermometer
• Class IIa	• X-ray films
• Class IIb	• Blood bags
• Class III	• Biological heart valves
• AIMD (active implantable medical device)	• Implantable pacemakers

Many patients require medical devices

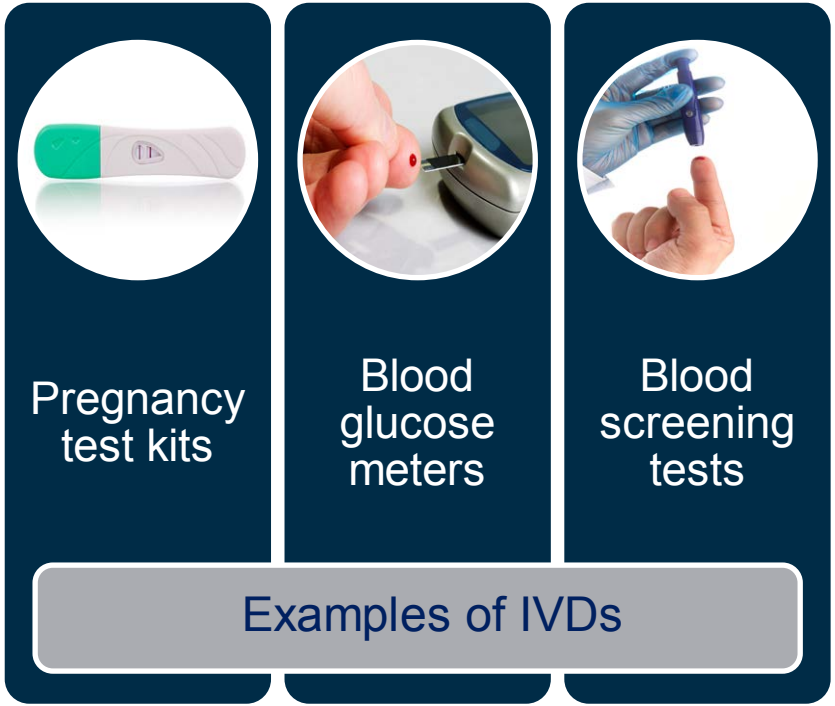




Tens of thousands of hip and knee procedures are performed every year. Ongoing safety and performance monitoring is important to ensure public safety after the device is made available on the market.

In vitro diagnostic tests

In vitro diagnostics have been regulated since July 2010 – with a four year transition period.



Risk classification rules - IVDs

Lower risk

Higher risk

IVD classification	Example
Class 1 IVD or Class 1 in-house IVD: no public health risk or low personal risk	Glucose meter
Class 2 IVD or Class 2 in-house IVD: low public health risk or moderate personal risk	Pregnancy and fertility self-testing kits
Class 3 IVD or Class 3 in-house IVD: moderate public health risk or high personal risk	Viral load and genotyping assays for HIV and Hepatitis C
Class 4 IVD or Class 4 in-house IVD: high public health risk	All tests used by the Australian Red Cross Blood Service for the testing of blood

Essential principles that govern devices

General principles

- Use of medical devices not to compromise health and safety
- Design and construction of medical devices to conform to safety principles
- Medical devices to be suitable for intended purpose
- Long-term safety
- Medical devices not to be adversely affected by transport or storage
- Benefits of medical devices to outweigh any side effects

See the following slide for an example

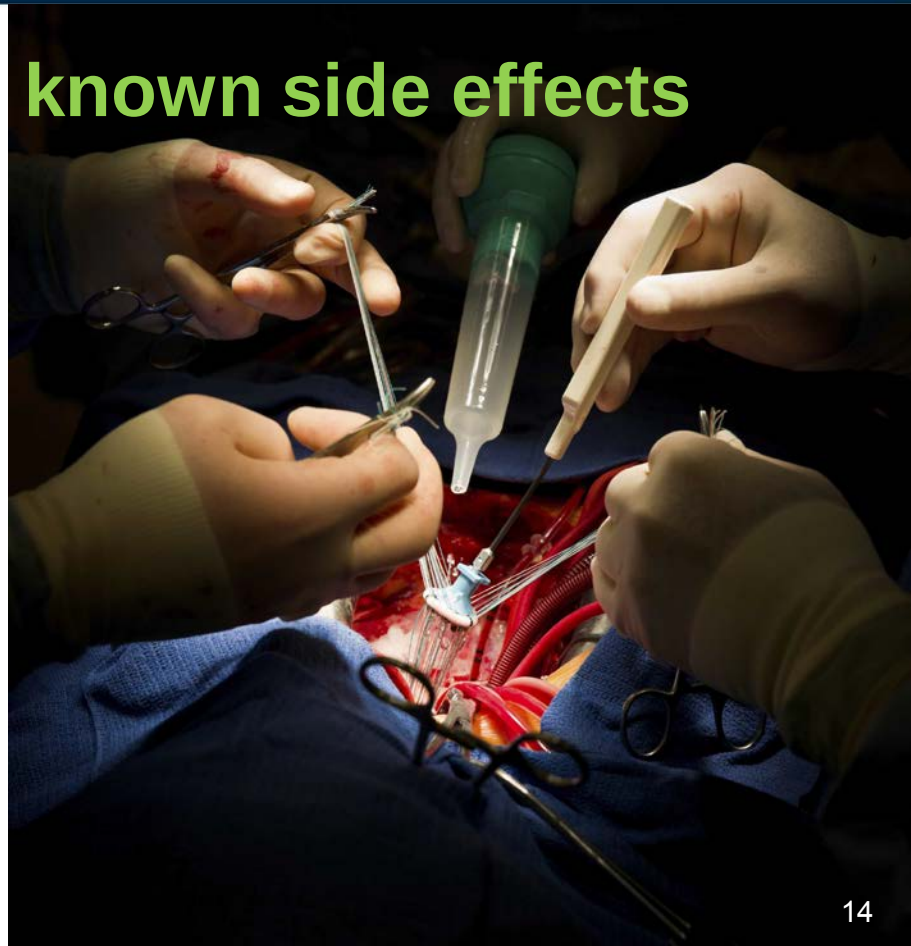
Assessing benefits versus known side effects

Left ventricular assist device

Complex medical devices used to assist with the ventricular flow of blood to the body in patients with significant heart failure

Associated with a number of known complications due their mechanical complexity and the patient groups in which they are used

Clinical evidence generated by the manufacturer could demonstrate that the benefits outweigh the side effects of the device by offering significant improvements in quality of life for users



Essential principles that govern devices

Principles about design and construction

- Chemical, physical and biological properties
- Infection and microbial contamination
- Construction and environmental properties
- Medical devices with a measuring function
- Protection against radiation
- Medical devices connected to or equipped with an energy source
- Information to be provided with medical devices
- Clinical evidence

See the following slide for an example

Devices and energy sources

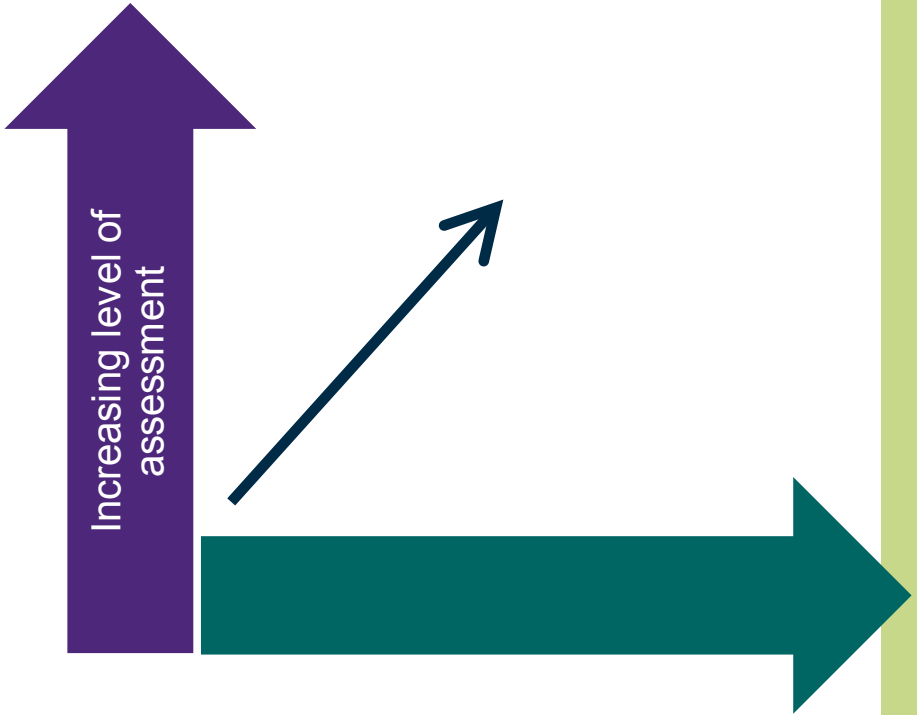
ECG patient monitor

Interprets the electrical activity of the heart using electrodes attached to the surface of the skin

Manufacturer must design and produce the device in a way that ensures that when the device is used correctly under normal conditions there is protection against faults

For example, patients and users are protected against the risk of accidental electric shock

Conformity assessment



Conformity assessments are all about the manufacturer!

They are used to ensure the essential principles and other regulatory requirements are met. The procedure for demonstrating this varies depending on the classification of the device.

Generally, the conformity assessment procedure is more rigorous the higher the risk class

Safety and performance – ongoing activities

- Reviews of technical and clinical information to ensure that compliance with the essential principles and conformity assessment procedures is demonstrated
- Testing to confirm compliance with the essential principles
- Inspections of manufacturer or sponsor records and documentation
- Audits of distribution records
- Audits of the traceability of raw materials used in the manufacture of therapeutic goods, tracking of component parts and the approved manufacturing processes
- Trend analysis and reporting to sponsors

Patients sometimes need special access

We have systems in place that provide access to unapproved medical devices.

Special Access Scheme (SAS)

Import and/or supply an unapproved therapeutic good for a single patient on a case-by-case basis

Regulation of medical software and mobile medical 'apps'

Software is becoming increasingly important in medical devices; its rapid evolution presents new and complex challenges for the regulatory agencies

A software product is considered a medical device if it fits the definition in s41BD of the *Therapeutic Goods Act 1989*.

A ***medical device*** is: any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;
- and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means

Regulation of medical software and mobile medical 'apps' (continued)

Examples:

- Analysers used for pathology/detection of disease, Patient monitors, Pacemakers, Infusion pumps.
- Smart phone apps that measure blood glucose levels and patient body temperature, X-ray image-processing software, Diagnostic software. Such software may be used with or in devices such as: Computers, Mobile phones, Tablets.
- However, a mobile phone, computer or tablet not intended by its manufacturer to be used for therapeutic purposes would not meet the definition of a medical device.

How is medical device software classified?

- Medical device software that is intended to control a device, or influence the functions of a device will generally fall into the same classification as that device.
- However, medical device software intended as an accessory to a medical device is classified separately from the device with which it is used.
- Regulation of medical device software and mobile medical apps that are medical devices is risk-based.
- The therapeutic goods legislation requires manufacturers of medical device software products (other than those which are classified as Class 1 - the lowest risk classification) to obtain Conformity Assessment certification, while all medical devices, irrespective of classification, are expected to meet the Essential Principles for safety and performance.
- The regulations make no distinction between different forms of software; all forms of software that meet the definition of a medical device must conform to the Essential Principles. For further information, please refer to Section 13 in Part 2 of the Australian Regulatory Guidelines for Medical Devices (ARGMD).

Future

- The TGA acknowledges the enormous complexity involved in attempting to regulate this area and continues to keep abreast of advancements in medical device technology.
- The TGA is a founding member of the International Medical Device Regulators Forum (IMDRF), a group of medical device regulators from around the world who meet regularly to accelerate international medical device regulatory harmonisation and convergence.
- Recognising that existing regulatory frameworks are not necessarily well structured to address the potential public health risks posed by standalone medical device software, in 2013 the IMDRF established a dedicated working group tasked with developing and harmonising approaches to the regulation of standalone medical device software (including mobile medical apps). The TGA is actively participating in this working group.
- Once the outcomes of the IMDRF working group are developed, the TGA may update this guidance in light of the Working Group's ultimate recommendations.

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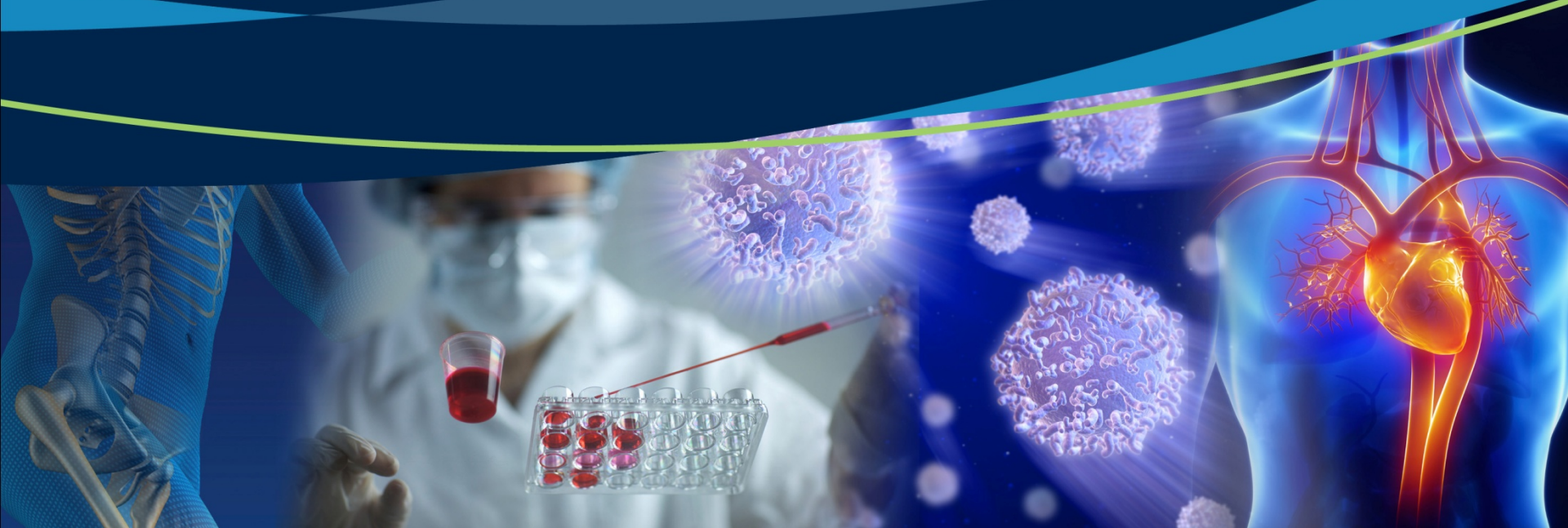
The regulation of biologicals in Australia



What are biologicals?

In Australia, 'biologicals' is the name for cell and tissue therapy products:

products in tissue banks

stem cell therapy products

excludes in vitro fertilisation products

excludes blood.

Other countries use different names for these products.

On 31 May 2011 a new regulatory framework was introduced to provide a legislative basis for the regulation of these products.

It applies different levels of regulation to products based on the risks associated with their use, and was designed to accommodate emerging technologies.

The Australian biologicals framework

Not regulated by the TGA*

- Fresh viable organs
- Assisted reproductive technologies (in vitro fertilisation)
- Fresh haematopoietic progenitor cells (bone marrow transplants)
- Cells and tissues made by a medical practitioner for a single patient under the care of that medical practitioner

*It is not practical to regulate these products. There are appropriate checks in place because of professional practice.

Regulated, but not as biologicals^

- Animal tissue products (xenotransplantation)
- Biological prescription medicines (vaccines, plasma derivatives)
- Labile blood and blood components
- Haematopoietic progenitor cells (non-fresh transplants)

^These are regulated as either medicines or medical devices

Regulated as biologicals

- Tissue-based products (skin, bone, ocular, cardiovascular)
- Cell-based products (T cell therapies, human stem cells)
- Combined cell and tissue products (collagen matrices for localised cell delivery)

These products are regulated as medicines

- Antibiotics
- Heparin
- Antivenoms
- Immunoglobulins
- Monoclonal antibodies
- Hormones such as insulin and growth hormone
- Blood products and clotting factors
- Vaccines
- Enzymes such as pancreatin

New and experimental products

Stem cell therapies are largely new and experimental

These offer great hope to people with serious incurable diseases:

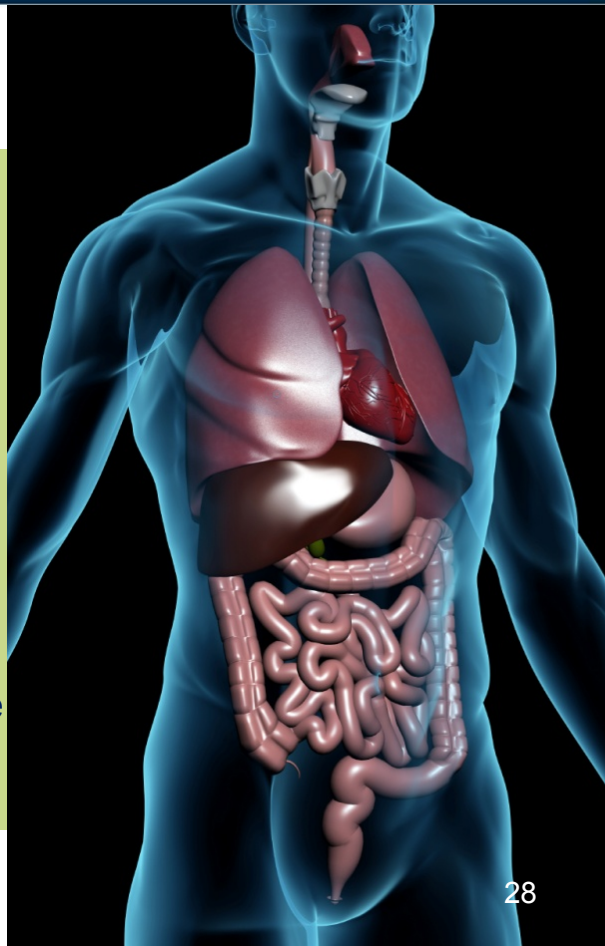
Parkinson's disease and other neurodegenerative diseases

spinal cord injury

heart disease, stroke and arthritis

Patients are sometimes desperate for these therapies to become a reality, however there are risks involved; the therapy is generally delivered via surgery, and the patients may require immunosuppressants for the rest of their life

But a lot of work is still needed to turn the research into safe and effective treatments



Clinical trials

One or more ethics committee approves every Australian clinical trial

- The TGA is **notified** of all clinical trials (the Clinical Trials Notification scheme – CTN)
- Some clinical trials are in the Clinical Trials eXemption scheme (CTX)

the details of these trials are examined, and commented on, by TGA staff

the ethics committee may then give approval to proceed

Clinical trials with biologicals in Australia offer access to new (but unproven) therapies.

Each trial has a research purpose, and patients need to provide informed consent

It is expected that most clinical trials for higher risk biologicals will take quite a few years

Higher and possibly unknown risks

Global clinical and regulatory experience with biologicals is more limited than with medicines

There is an increased risk of infectious disease transmission. It is difficult to obtain complete history for deceased donors

Because of limited clinical experience with biologicals unforseen side effects are more common

Regulation takes into account risk

- **A risk classification system is used for biologicals to be included on the Australian Register of Therapeutic Goods (ARTG)**
- **The risk class depends on:**
  - how far removed they are from their naturally occurring state (how much they have been manipulated during the extraction and production process)
  - how closely the intended use matches the natural biological function

Centrifugation is an example of minimal manipulation of a biological. Genetic modification is an example of high manipulation

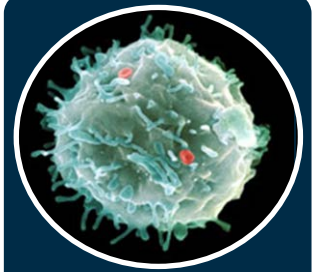
The main risk with using biologicals is the spread of infection

Biologicals are grouped into classes

Examples:

Acellular skin for wound covering

Class 2



Mesenchymal stem cell for treatment of graft-versus-host disease

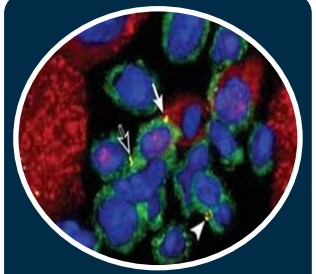
Class 3

Demineralised bone mixed with carrier

Class 3

Dermal fibroblasts transformed for skeletal muscle repair in primary myopathy

Class 4



Genetically-modified T cells used to treat specific virus infections

Class 4

Current uses of biologicals

Corneal transplants can restore sight in pati whose eyes have been affected by disease injury or infection

Skin grafts are used for patients with burns

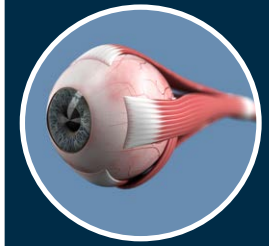
Biological heart valves

- **Bone transplants are o**ften donated by hip replacement patients
- **Tendon transplants are used to help restor mobility to arms, elbows, hands etc**

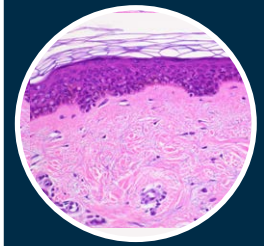
Turning human stem cells into heart cells, pancreatic beta cells, intestinal cells, liver and nerve cells

Current biologicals

Human tissues currently in Australian tissue banks:

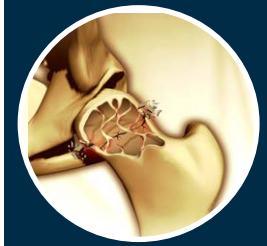


Ocular tissue



Skin

Cardio-vascular tissue



Bone and tendons

Australian tissue banks are principally owned and operated on a not-for-profit basis by charitable organisations or state governments

The process for inclusion of biologicals in the ARTG

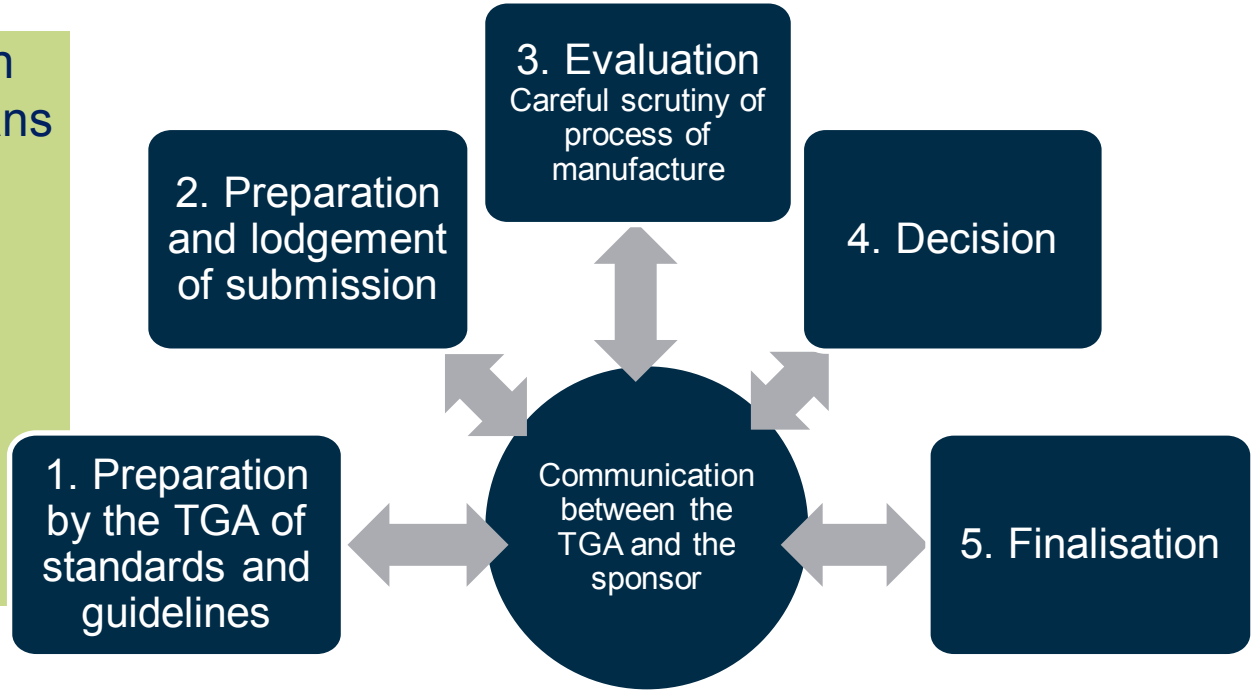
Evaluation is undertaken by scientists and clinicians who look at data on:

quality

safety

efficacy

More information about what this means is provided later in the presentation



The Advisory Committee on Biologicals provides independent expert advice to the TGA about issues related to biologicals

Exceptional release provisions

The TGA can apply exceptional release provisions to treat life-threatening conditions

For example, a paediatric heart valve becomes available at a valve bank for a critically ill baby but it is not possible to wait 10 days for tissue microbial testing results

This paediatric heart valve does not meet the required safety standards or current manufacturing standards but the TGA releases the product due to the exceptional circumstances

Postmarket monitoring

Reporting adverse events

Adverse event reporting relates to unintended harmful effects or new information that contradicts existing knowledge about the quality, safety or efficacy of a biological

For biologicals, the reporting process is based on existing processes established within the TGA

- Sponsors are required to monitor, record and report all adverse events to the TGA
- Medical practitioners, patients, and others are also encouraged to report

The TGA will investigate and respond to adverse events as appropriate

In addition to the mandatory reporting requirements there is also a voluntary incident reporting scheme where any incidents involving a biological can be reported.

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Regulating the manufacture of therapeutic goods

Checking the quality of therapeutic goods

The TGA monitors and assesses manufacturers to ensure that therapeutic goods supplied in Australia are manufactured to a high standard

The emphasis and depth of manufacturer inspections, as well as the frequency of inspections, are guided by the inherent risks of the product and the method of manufacture. We also take into account the compliance and inspection history of the manufacturer

How do we do this?

On-site inspections of manufacturers and compliance verifications (paper-based assessments)

Australian and overseas manufacturers are assessed prior to supply of goods and are then regularly reviewed

Inspections against the relevant Code of Good Manufacturing Practice (GMP) or Standard (for devices) which describes the range of conditions required for the safe, sterile production of goods

Quality manufacturing

Higher risk products

- Sterile medicines, including active pharmaceutical ingredients
- Single step sterilisers
- Non-sterile medicines containing antibiotics, steroids or antineoplastics
- Primary collection, processing and storage sites for blood, including human haematopoietic stem cells
- Tissue banks with complex processing
- Cellular therapies
- Medical devices - Class III and Active Implantable Medical Devices (AIMD)

Pacemakers are regulated as AIMDs

Plasmapheresis

Medium risk products

- Non-sterile medicines, including herbal products
- Secondary blood collection and separation sites (including sites collecting plasma only or platelets)
- Tissue banks with low manipulation
- Other medical devices

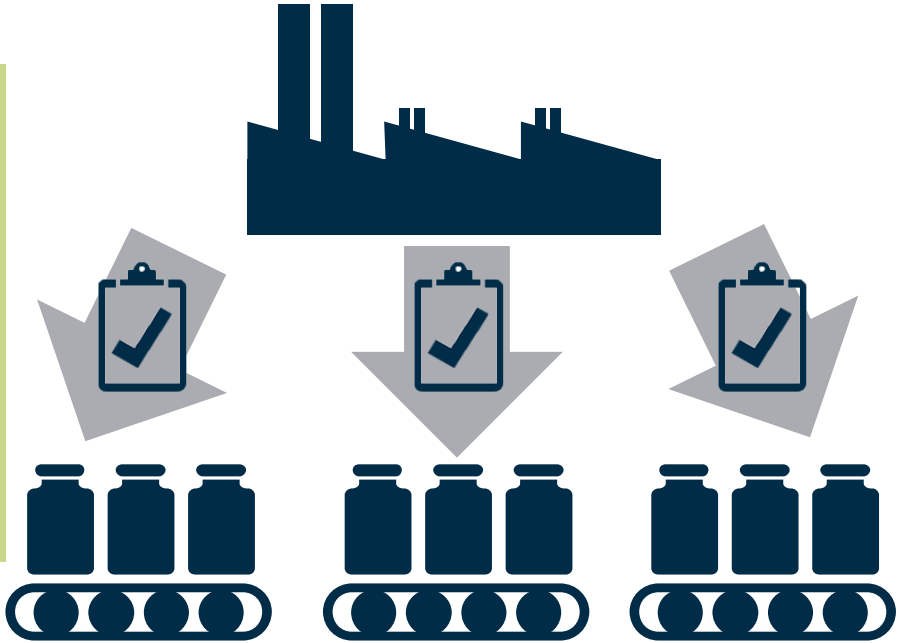
Lower risk products

- Minerals, vitamins, fish oils and other supplements
- Sunscreens
- Medicinal gases
- Other blood collection sites including mobile units
- Homeopathic medicines

The basis of Good Manufacturing Practice

A basic tenet of GMP is that:

- Simply testing a product after manufacture is not sufficient to ensure product quality
- Quality must be built into each batch of a product during all stages of the manufacturing process



Looking at the actual product

GMP requirements cover:

- How products are manufactured, packaged, labelled and stored
- How therapeutic goods are tested to ensure that products are of a suitable quality, including the final evaluation and approval for use by the manufacturer of each batch made

The manufacturer must:

- Have a quality management system in place under which manufacturing activities are controlled
- Include in the system personnel involved in the control of therapeutic goods manufacturing and how they are trained
- Provide information on how premises used in the manufacture of goods are designed, operated, maintained and controlled
- Control manufacturing activities through the use of written procedures and instructions
- Record manufacturing events through comprehensive record keeping practices

Inspections include verification that:

All manufacturing processes are clearly defined and regularly reviewed

Records of all manufacturing activities are kept

Critical manufacturing processes and changes are validated

All starting materials and finished products are sampled, tested and approved for use using appropriate methods

Written instructions for all tasks are developed and available

Batches are certified as fit-for-purpose prior to distribution

Inspecting Australian manufacturers

In Australia, the TGA manages annually:

- ~400 licences for manufacturing, supply and distribution sites
- ~450 sites
- ~250 inspections of sites

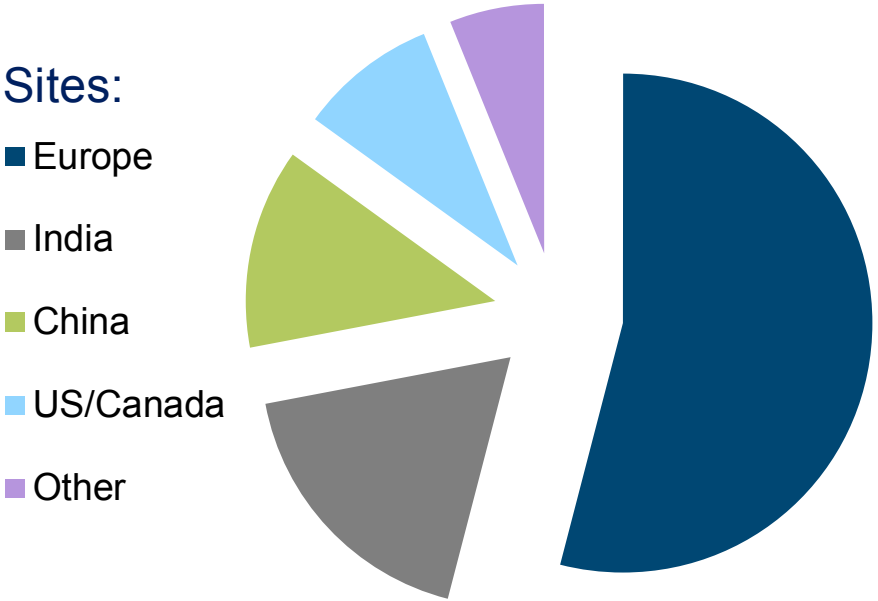
*statistics per annum, current as of July 2013

Which countries supply to Australia?

Therapeutic goods are manufactured and supplied in a global market

This includes both finished goods and ingredients

Countries who manufacture or supply to Australia include:

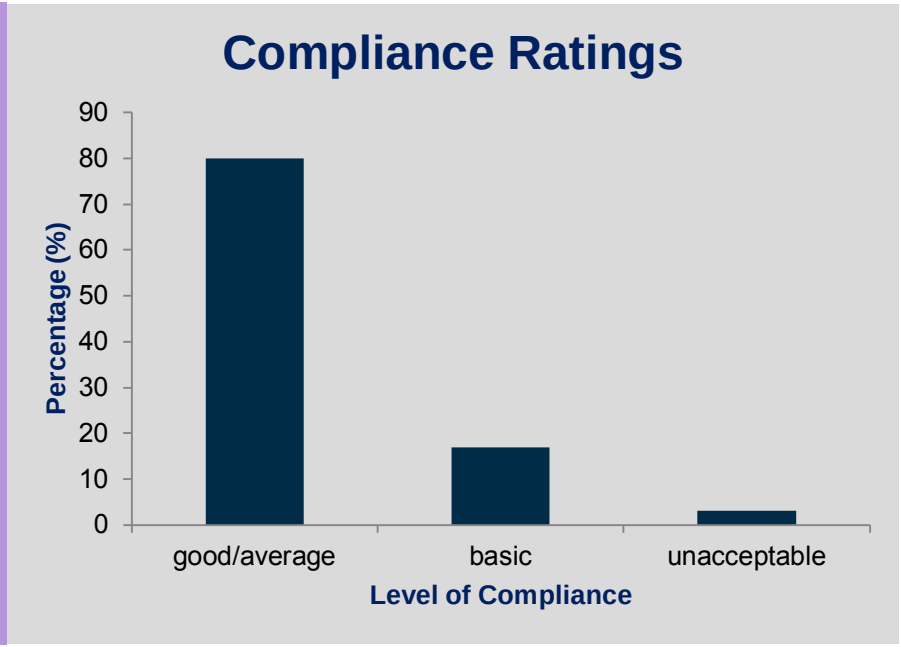


*current as of July 2013

Inspecting international manufacturers

TGA inspection and certification of overseas sites

- ~2,000 manufacturers > 2,500 sites
- ~3,500 clearances
- 150-200 on-site inspections
- Increasing number of compliance verifications (using inspection reports from other agencies)



*statistics are per annum, current as of July 2013

The future of manufacturing

- Manufacturing is being expanded to developing countries
- Faster access to products for Australians
- Multi-step manufacture of products is common
- Complex supply chains which may span many different countries
- Challenges with different languages

International harmonisation

- International harmonisation of standards and inspections allows for a shared workload with regulators in other countries
- It may include:
  - joint inspections with overseas partners
  - shared inspection scheduling
  - sharing of information, reports and manufacturer information
  - mutual recognition of codes of GMP and standards

Recall actions

A recall action is taken to resolve a problem with a therapeutic good already supplied in the market when there are issues or deficiencies in relation to safety, quality, efficacy (performance) or presentation. There are three distinct recall actions:

Recall

July 2013: one batch of Febridol Paracetamol 500 mg,100 tablet bottles recalled due to possibility of containing a foreign tablet

Recall for product correction

June 2013: Medtronic Paradigm insulin infusion sets recalled for product correction due to a potential safety issue if insulin or other fluids came in contact with the set's connector

Hazard alert

August 2013: hazard alert for the PyroTitan humeral resurfacing arthroplasty device, due to potential to break after being implanted

Search Recall actions

- The SARA database is searchable for therapeutic good recall action notifications that include recalls, recalls for product correction and hazard alerts.
- Recall actions are included into the SARA two days (excluding weekends) after the decision between the responsible entity and the TGA, to commence the recall action. This allows time for the responsible entity (sponsor/supplier/importer) to distribute the recall communication.
- In certain circumstances (e.g. consumer level recall actions and recall actions involving implantable medical devices), notices are also published on the alerts page.

Subscribe to the TGA information services to stay up-to-date: www.tga.gov.au

Receive information on:

- Safety alerts
- Recall actions
- Medicines Safety Update
- Medical Devices Safety Update
- Consultations
- Publications
- Scheduling

Thank you

Please feel free to email your questions to-

Mandvi.bharadwaj@tga.gov.au

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